

Serial No.: 09/746,036

Attorney Docket No.: 3363

AMENDMENTS

Amendments to the Specification

Please replace the paragraph on page 9, line 8 with the following amended paragraph:

Methods for making and using molecular probe arrays, particularly nucleic acid probe arrays are also disclosed in, for example, U.S. Patent Numbers 5,143,854, 5,242,974, 5,252,743, 5,324,633, 5,384,261, 5,405,783, 5,409,810, 5,412,087, 5,424,186, 5,429,807, 5,445,934, 5,451,683, 5,482,867, 5,489,678, 5,491,074, 5,510,270, 5,527,681, 5,527,681, 5,541,061, 5,550,215, 5,554,501, 5,556,752, 5,556,961, 5,571,639, 5,583,211, 5,593,839, 5,599,695, 5,607,832, 5,624,711, 5,677,195, 5,744,101, 5,744,305, 5,753,788, 5,770,456, 5,770,722, 5,831,070, 5,856,101, 5,885,837, 5,889,165, 5,919,523, 5,922,591, 5,925,517, 5,658,734, 6,022,963, 6,150,147, 6,147,205, 6,153,743, 6,140,044 and D430024, all of which are incorporated by reference in their entireties for all purposes. Typically, a nucleic acid sample is labeled with a signal moiety, such as a fluorescent label. The sample is hybridized with the array under appropriate conditions. The arrays are washed or otherwise processed to remove non-hybridized sample nucleic acids. The hybridization is then evaluated by detecting the distribution of the label on the chip. The distribution of label may be detected by scanning the arrays to determine fluorescence intensities distribution. Typically, the hybridization of each probe is reflected by several pixel intensities. The raw intensity data may be stored in a gray scale pixel intensity file. The GATC™ Consortium has specified several file formats for storing array intensity data. The final software specification is available on the GATC Consortium's website at www.gateconsortium.org and is incorporated herein by reference in its entirety. The pixel intensity files are usually large. For example, a GATC™ compatible image file

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may be approximately 50 Mb if there are about 5000 pixels on each of the horizontal and vertical axes and if a two byte integer is used for every pixel intensity. The pixels may be grouped into cells (see, GATCTTM software specification). The probes in a cell are designed to have the same sequence (i.e., each cell is a probe area). A CEL file contains the statistics of a cell, e.g., the 75 percentile and standard deviation of intensities of pixels in a cell. The 75 percentile of pixel intensity of a cell is often used as the intensity of the cell. Methods for signal detection and processing of intensity data are additionally disclosed in, for example, U.S. Patents Numbers 5,547,839, 5,578,832, 5,631,734, 5,800,992, 5,856,092, 5,936,324, 5,981,956, 6,025,601, 6,090,555, 6,141,096, 6,141,096, and 5,902,723. Methods for array based assays, computer software for data analysis and applications are additionally disclosed in, e.g., U.S. Patent Numbers 5,527,670, 5,527,676, 5,545,531, 5,622,829, 5,631,128, 5,639,423, 5,646,039, 5,650,268, 5,654,155, 5,674,742, 5,710,000, 5,733,729, 5,795,716, 5,814,450, 5,821,328, 5,824,477, 5,834,252, 5,834,758, 5,837,832, 5,843,655, 5,856,086, 5,856,104, 5,856,174, 5,858,659, 5,861,242, 5,869,244, 5,871,928, 5,874,219, 5,902,723, 5,925,525, 5,928,905, 5,935,793, 5,945,334, 5,959,098, 5,968,730, 5,968,740, 5,974,164, 5,981,174, 5,981,185, 5,985,651, 6,013,440, 6,013,449, 6,020,135, 6,027,880, 6,027,894, 6,033,850, 6,033,860, 6,037,124, 6,040,138, 6,040,193, 6,043,080, 6,045,996, 6,050,719, 6,066,454, 6,083,697, 6,114,116, 6,114,122, 6,121,048, 6,124,102, 6,130,046, 6,132,580, 6,132,996, 6,136,269 and attorney docket numbers 3298.1 and 3309, all of which are incorporated by reference in their entireties for all purposes.

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Please replace the paragraph on page 11, line 4 with the following amended paragraph:

Nucleic acid probe array technology, use of such arrays, analysis array based experiments, associated computer software, composition for making the array and practical applications of the nucleic acid arrays are also disclosed, for example, in the following U.S. Patents and Patent Applications: 07/838,607 (currently abandoned), 07/883,327 (currently abandoned), 07/978,940 (currently abandoned), 08/030,138 (currently abandoned), 08/082,937 (currently abandoned), 08/143,312 (currently abandoned), 08/327,522 (currently abandoned), 08/376,963 (currently abandoned), 08/440,742 (currently abandoned), 08/533,582 (currently pending), 08/643,822 (currently abandoned), 08/772,376 6,309,822, 09/013,596 6,294,327, 09/016,564 (currently abandoned), 09/019,882 (currently abandoned), 09/020,743 6,420,108, 09/030,028 6,335,161, 09/045,547 6,201,639, 09/060,922 (currently abandoned), 09/063,311 (currently abandoned), 09/076,575 (currently pending), 09/079,324 (currently pending), 09/086,285 6,303,301, 09/093,947 (currently abandoned), 09/097,675 6,203,983, 09/102,167 (currently abandoned), 09/102,986 (currently abandoned), 09/122,167 6,229,911, 09/122,169 6,484,183, 09/122,216 6,269,846, 09/122,304 6,188,783, 09/122,434 6,308,170, 09/126,645 (currently abandoned), 09/127,115 6,197,508, 09/132,368 (currently abandoned), 09/134,758 6,223,127, 09/138,958 6,306,643, 09/146,969 6,228,585, 09/148,210 (currently abandoned), 09/148,813 (currently abandoned), 09/170,847 6,185,030, 09/172,190 6,262,216, 09/174,364 6,489,096, 09/199,655 (currently pending), 09/203,677 6,258,536, 09/256,301 6,177,248, 09/285,658 6,582,906, 09/294,293 6,171,793, 09/318,775 6,271,957, 09/326,137 6,653,071, 09/326,374 6,218,803, 09/341,302 (currently abandoned), 09/354,935

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6,185,561, 09/358,664 6,495,320, 09/373,984 (currently pending), 09/377,907 (currently abandoned), 09/383,986 6,545,264, 09/394,230 (currently pending), 09/396,196 (allowed), 09/418,044 6,486,286, 09/418,946 (currently abandoned), 09/420,805 6,287,778, 09/428,350 6,361,947, 09/431,964 6,340,565, 09/445,734 6,368,799, 09/464,350 (currently abandoned), 09/475,209 6,612,737, 09/502,048 (currently abandoned), 09/510,643 6,335,170, 09/513,300 (currently abandoned), 09/516,388 (currently abandoned), 09/528,414 (currently pending), 09/535,142 6,403,317, 09/544,627 6,647,341, 09/620,780 (currently pending), 09/640,962 (currently abandoned), 09/641,081 (currently pending), 09/670,510 6,505,125, 09/685,011 (currently abandoned), and 09/693,204 (currently pending) and in the following Patent Cooperative Treaty (PCT) applications/publications: PCT/NL90/00081 (entered National Stage), PCT/GB91/00066 (entered National Stage), PCT/US91/08693 (entered National Stage), PCT/US91/09226 (currently abandoned), PCT/US91/09217 (currently abandoned), WO/93/10161 (currently abandoned), PCT/US92/10183 (entered National Stage), PCT/GB93/00147 (entered National Stage), PCT/US93/01152 (entered National Stage), WO/93/22680 (currently abandoned), PCT/US93/04145 (entered National Stage), PCT/US93/08015 (entered National Stage), PCT/US94/07106 (entered National Stage), PCT/US94/12305 (entered National Stage), PCT/GB95/00542 (entered National Stage), PCT/US95/07377 (entered National Stage), PCT/US95/02024 (entered National Stage), PCT/US96/05480 (entered National Stage), PCT/US96/11147 (entered National Stage), PCT/US96/14839 (entered National Stage), PCT/US96/15606 (currently inactive), PCT/US97/01603 (entered National Stage), PCT/US97/02102 (entered National Stage), PCT/GB97/005566 (currently inactive), PCT/US97/06535 (entered National Stage),

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PCT/GB97/01148 (entered National Stage), PCT/GB97/01258 (entered National Stage),
PCT/US97/08319 (entered National Stage), PCT/US97/08446 (currently abandoned),
PCT/US97/10365 (currently inactive), PCT/US97/17002 (entered National Stage),
PCT/US97/16738 (currently inactive), PCT/US97/19665 (currently abandoned),
PCT/US97/20313 (entered National Stage), PCT/US97/21209 (entered National Stage),
PCT/US97/21782 (currently abandoned), PCT/US97/23360 (entered National Stage),
PCT/US98/06414 (entered National Stage), PCT/US98/01206 (entered National Stage),
PCT/GB98/00975 (entered National Stage), PCT/US98/04280 (currently abandoned),
PCT/US98/04571 (entered National Stage), PCT/US98/05438 (entered National Stage),
PCT/US98/05451 (entered National Stage), PCT/US98/12442 (entered National Stage),
PCT/US98/12779 (currently abandoned), PCT/US98/12930 (currently abandoned),
PCT/US98/13949 (currently abandoned), PCT/US98/15151 (entered National Stage),
PCT/US98/15469 (entered National Stage), PCT/US98/15458 (entered National Stage),
PCT/US98/15456 (entered National Stage), PCT/US98/16971 (entered National Stage),
PCT/US98/16686 (entered National Stage), PCT/US99/19069 (entered National Stage),
PCT/US98/18873 (entered National Stage), PCT/US98/18541 (entered National Stage),
PCT/US98/19325 (currently abandoned), PCT/US98/22966 (entered National Stage),
PCT/US98/26925 (entered National Stage), PCT/US98/27405 (currently inactive) and
PCT/IB99/00048 (currently abandoned), all of which are incorporated by reference in
their entireties for all purposes. All the above cited patent applications and other
references cited throughout this specification are incorporated herein by reference in their
entireties for all purposes.

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Please replace the paragraph on page 13, lines 6-14 with the following amended paragraph:

In the preferred embodiment, oligonucleotide probes are synthesized directly on the surface of the array using photolithography and combinatorial chemistry as disclosed in several patents previously incorporated by reference. In such embodiments, a single square-shaped feature on an array contains one type of probe. Probes are selected to be specific against desired target. Methods for selecting probe sequences are disclosed in, for example, U.S. Patent Application Nos. 09/718,295 filed November 21, 2000; [[_____, Attorney Docket Number 3359; _____, filed November 21, 2000,]] ~~Attorney Docket Number 3367~~, 09/721,042 filed November 21, 2000, and [[_____, Attorney Docket Number 3373,]] U.S. Provisional Application Serial No. 60/252,617 filed November 21, 2000, all incorporated herein by reference in their entireties for all purposes.

Please replace the paragraph on page 15, line 20 with the following amended paragraph:

Computer software products may be written in any of various suitable programming languages, such as C, C++, C# (Microsoft®), Fortran, Perl, MatLab (MathWorks, ~~www.mathworks.com~~), SAS, SPSS and Java. The computer software product may be an independent application with data input and data display modules. Alternatively, the computer software products may be classes that may be instantiated as distributed objects. The computer software products may also be component software such as Java Beans (Sun Microsystems), Enterprise Java Beans (EJB, Sun Microsystems), Microsoft® COM/DCOM (Microsoft®), etc.

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Please replace the paragraph on page 18, line 21 with the following amended paragraph:

The parameters may be estimated by maximizing $\sum (s(i) + c(j, k) + x(k, l))$ (i.e., maximizing the true effect). Alternatively, the parameters may also be estimated by minimizing $\sum (Y(i, j, k, l) - s(i) - c(j, k) - x(k, l))$. Because $x(k, l)$ is the *log(relative transcript level)*, $\sum x(k, l) = 0$. Since $\sum x(k, l) = 0$, this may be equivalent to maximize $\sum (s(i) + c(j, k))$. In some embodiments, the chip effect, $s(i)$ may be estimated independently, for example, by spiking each chip with known concentration of a control transcript or by using normalization controls such as probes against maintenance genes. Exemplary methods for estimating normalization factor to account for chip to chip variation are disclosed in, for example, U.S. Patent Application Serial Number 09/735,574 [_____, Attorney Docket Number 3364]], filed on December 12, 2000, which is incorporated herein in its entirety by reference for all purposes.